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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/842,547	04/26/2001	Michael A. Adams	PTQ-0031	7618

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TOWNSEND AND TOWNSEND AND CREW, LLP
TWO EMBARCADERO CENTER
EIGHTH FLOOR
SAN FRANCISCO, CA 94111-3834

EXAMINER	
PAK, JOHN D	

ART UNIT	PAPER NUMBER
1616	

DATE MAILED: 05/10/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/842,547	ADAMS ET AL.	
	Examiner	Art Unit	
	JOHN D PAK	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,8,13,16-19,22 and 33-40* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,8,13,16-19,22 and 33-40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Claims 1-5, 8, 13, 16-19, 22 and 33-40 are pending in this application.

It is noted for the record that the elected species under examination here is GTN, also known as glyceryl trinitrate or nitroglycerine. The pending claims will presently be examined to the extent that that they read on the elected subject matter, supra.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-5, 8, 13, 16-19, 22 and 33-40 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Amended claims 1-5, 8, 13, 16-19 and 22 (independent claims only were actually amended, but dependent claims read on such amendments) recite or read on "low dose is 3 to 10,000 fold lower than a dose of said nitric oxide mimetic that produces vasodilation." This is a somewhat confusing or indefinite claim feature. The problem is with the term "vasodilation." Vasodilation is widening of the lumen of any blood vessel. Since blood vessels supply blood to tumor cells, the quoted claim feature is confusing and indefinite. An inventive amount that is chosen (for example, 0.1 mg sublingual administration, noted on the specification p. 13 as being inventive) could be vasodilative for a tumor blood vessel. Therefore, one skilled in the art would find the above quoted

claim feature to be confusing and indefinite, which would render the metes and bounds of "low dose" unclear.

Newly added claims 33-40 recite doses, wherein the unit of the dose is "M." This symbol means moles per liter. However, moles per liter is a unit of concentration, not a unit of dose. A dose is an exact amount of medicine given to a patient. Here, the recited concentration is an incomplete description of the "dose," because the dose will depend on how much of the, for example, 10^{-14} M solution is given, e.g. 10 ml or 200 ml. Therefore, the use of "dose" in claims 33-40 is confusing. The Examiner suggests incorporation of the "3 to 10,000 fold lower" feature of claim 1, in addition to the concentration feature of the instant rejected claims.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 4-5, 8 are rejected under 35 U.S.C. 102(b) as being anticipated by Ushmorov et al.[1]

Ushmorov et al. explicitly disclose treating human leukemic T-cell lines (p. 2343, Materials and Methods) with 2 X 10^{-4} M GTN (Fig. 1, Fig. 2, P. 2345, left column, lines

1-4; see also p. 2342, right column, last partial paragraph, first sentence). 33% apoptosis is obtained (p. 2345, left column, lines 1-3). Effective treatment of leukemia patients by using NO donors or other agents to induce apoptosis through damage of mitochondrial functions in leukemic cells is disclosed (p. 2350, right column, last sentence).

Claims 1, 4-5 and 8 are readable on in vitro methods. The "low dose is 3 to 10,000 fold lower than a dose of said nitric oxide mimetic that produces vasodilation" feature is interpreted without material weight in an in vitro method since in vitro leukemic cell samples in Ushmorov's experiments would not manifest vasodilation. Inhibition of metastases and development of resistance to antimalignant therapeutic modalities is inherent in a cell sample, viz. contained, previously untreated cell samples do not metastasize or develop resistance. The same can be said for development of a more aggressive malignant cell phenotype in the cells, further in view of apoptosis activity. Note, claim 4 does not actually require administering an anti-VEGF agent. The Examiner interprets "upon administration" as having a scope of "if and when administered, " which is not the same thing as "administering nitroglycerine and then administering an anti-VEGF agent." The same interpretation is made with respect to claim 5's "cells exposed to factors which lower cellular nitric oxide mimetic activity." This feature does not explicitly require exposing the cells to said factors. It merely

[1] Blood, Vol. 93, No. 7. This journal was received by the PTO library on 3/29/1999.

states, or is readable on, cells that if exposed sometime in the future, development of a malignant cell phenotype would be inhibited.

Interpreted as discussed above, the claims are anticipated by Ushmorov et al.

Claims 1-5, 8, 13, 16-18, 19 are rejected under 35 U.S.C. 102(b) as being anticipated by Derwent abstract, accession no. 1998-313779 (abstracting DE 19732323).

Derwent abstract 1998-313779 explicitly discloses local administration of 0.012-0.025 mg of nitroglycerine per kg of patient body weight for improving the local effect of drugs for cancer treatment.

The claimed feature, "wherein the low dose is 3 to 10,000 fold lower than a dose of said nitric oxide mimetic that produces vasodilation" is noted. However, the cited reference explicitly discloses local application of nitroglycerine, i.e. directly onto the tumor. Such local administration would not produce vasodilation outside of the locally administered area such as targeted tumor mass[2]. *To the extent that* "vasodilation"

[2] There is evidence that at the tumor site, there may be a contrary effect, i.e. no vasodilation of tumor vasculature. See applicant's cited reference, Pallavicini et al., Radiation Oncology Biology Physics, Vol. 9(9), 1983, page 1322, Table 1 (12% blood flow decrease after GTN administration). This goes to the Examiner's position that the local administration as disclosed by the Derwent abstract, supra, meets applicant's claim feature wherein the dose is one that is at least 3 fold lower than a vasodilative dose at the local level. Since the dose at the local level does not produce vasodilation of tumor blood vessels, it is at least 3 fold lower than a vasodilative dose.

applies to systemic or coronary vasodilation, i.e. it does not apply to vasodilation of tumor blood vessels, the claim feature is met.

The cited reference administers the nitroglycerine + cancer drug to subjects with cancer, so such subjects satisfy "at risk for or suffering from a malignant cell phenotype." Inhibition of metastases and development of resistance to antimalignant therapeutic modalities is inherent since the same substance is administered to the same subject at the same dosage. The same can be said for development of a more aggressive malignant cell phenotype in the cells. Note, claim 4 does not actually require administering an anti-VEGF agent. The Examiner interprets "upon administration" as having a scope of "if and when administered, " which is not the same thing as "administering nitroglycerine and then administering an anti-VEGF agent." The same interpretation is made with respect to claim 5's "cells exposed to factors which lower cellular nitric oxide mimetic activity." This feature does not explicitly require exposing the cells to said factors. It merely states, or is readable on, cells that if exposed sometime in the future, development of a malignant cell phenotype would be inhibited.

For these reasons, the above noted claims are rejected by Derwent abstract 1998-313779.

Rejections set forth in the previous Office Action (mail date 7/14/03) wherein Umansky et al. and/or Bonavida et al. are relied upon are withdrawn in view of applicant's declaration under 37 CFR 1.131.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

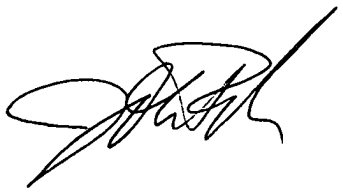
A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to JOHN PAK whose telephone number is **(571)272-0620, effective February 3, 2004.** The Examiner can normally be reached on Monday to Friday from 8 AM to 4:30 PM.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's SPE, Thurman Page, can be reached on (571)272-0602, effective February 3, 2004.

The fax phone number for the organization where this application or proceeding is assigned is (703)872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571)272-1600.



JOHN PAK
PRIMARY EXAMINER
GROUP 1600